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RULE 17.1

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I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1264/Del/2002*** *dated* ***16th December 2002.***

Witness my hand this 13th day of January 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

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1264-02

16 DEC 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR PREPARING AN EXTENDED RELEASE FORMULATION OF PHENYTOIN SODIUM"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. DEEPAK MURPANI

b. ASHISH MADAN

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

DUPLICATE

6. Following declaration was given by the inventors in the convention country:

We, DEEPAK MURPANI, ASHISH MADAN of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Deepak Murpani

(DEEPAK MURPANI)

b.

(ASHISH MADAN)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **685795** dated :**15.11.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **13TH** day of **December, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2 1264-02

The Patents Act, 1970 16 DEC 2002

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

A PROCESS FOR PREPARING AN EXTENDED RELEASE FORMULATION OF PHENYTOIN SODIUM

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for preparing extended release pharmaceutical composition comprising a blend of phenytoin sodium and hydrophilic polymer(s).

Phenytoin sodium is a known antiepileptic compound. Phenytoin, phenytoin sodium and procedures for their manufacture are well known, for example Kao et al., US Patent No. 4,696,814; Fawzi et. Al., US Patent No. 4,642,316 and Henze et al., US Patent No. 2,409,754, all of which are incorporated herein by reference.

Phenytoin sodium is commercially available as 30 mg and 100 mg capsules marketed by Parke Davis, sold under the brand name Dilantin®. These capsules contain lactose, confectioner's sugar, talc, magnesium stearate and phenytoin sodium as loose powder. The capsules are sealed with a band. Drug release problems associated with these pharmaceutical compositions have resulted in numerous recalls for failure to meet dissolution requirements. Moreover, Dilantin® requires multiple, repetitive dosing intervals. A dose of 100 mg of Dilantin requires a capsule size #3 (230 mg), therefore in order to incorporate a larger dose of the drug using Dilantin capsules, the size of the capsules would have to increased; thus making it patient incompliant.

Extended release oral capsules containing 200mg and 300mg phenytoin sodium are also available commercially under the brand name Phenytek®. These capsules contain phenytoin sodium in an erodible matrix, comprising povidone, hydroxyethyl cellulose, microcrystalline cellulose, magnesium oxide, colloidal silicon dioxide and magnesium stearate as described in Mylan's US Patent No. 6,274,168 and its continuation in part application US 20010043945. These extended release oral capsules are prepared by mixing phenytoin sodium with diluents, binder(s), alkaline pH modifier(s), or a combination thereof, and then granulating with an aqueous solvent, which may or may not contain a binder(s). The dried granules are milled and finally blended with other excipients. The blend is filled into capsules or compressed into tablets. The tablets may then be additionally coated and/or filled into capsules.

The present invention provides a simple, economical and easy process for manufacturing extended release phenytoin oral capsules.

Thus, in the present invention extended-release capsules are formulated by employing a simple process, which does not involve extra steps of granulation, drying, milling, compression and band-sealing after filling in capsules and is still capable of imparting extended-release properties.

Accordingly, it is an object of the present invention to provide an extended release formulation for phenytoin sodium that can deliver 100-300mg of the drug in a single unit dosage form without batch-to-batch variation.

It is another object of the present invention to provide an extended release formulation for phenytoin sodium using a simple process, which can be easily adapted for lower or higher strengths.

It is a further object of the present invention to provide an extended release formulation for phenytoin sodium that contains a high dose medicament and is of an acceptable size, convenient for oral administration.

In the present invention the above objectives have been achieved by filling a blend of phenytoin sodium and hydrophilic polymer(s) as powder into hard gelatin capsules. Powder filling eliminates the steps of granulation, drying, milling and compaction thus making the process simple, cost effective and time saving. The use of hydrophilic polymers effectively controls the release rate of the drug without significant batch-to-batch variability initially as well as after a storage period of 3 months at accelerated conditions of temperature and humidity. Further, filling of blend of the present invention into capsules does not require an additional process of band sealing.

Therefore, the extended release pharmaceutical composition of the present invention comprises a blend of phenytoin sodium and hydrophilic polymer(s), wherein the blend forms a matrix on coming in contact with aqueous media, and wherein said matrix retains at least about 20% phenytoin after 1 hour. The hydrophilic polymer is selected in such a way that it brings about batch-to-batch reproducibility in the dissolution profile of the

pharmaceutical composition of the present invention. While not intending to be limited by any theory, it is believed that upon oral ingestion of the extended-release powder-filled capsules of the invention, in an acid aqueous environment, such as the stomach, water penetrates the capsule shell initiating surface hydration of the hydrophilic polymer blend to form a gel layer. Erosion of the gel layer gradually exposes more dry powder that hydrates to form a matrix. Drug is then released by diffusion through the matrix over an extended period of time.

The matrix formed retains at least about 20% phenytoin after 1 hour. Preferably the said matrix retains at least about 30% phenytoin after 1 hour and more preferably, the said matrix retains at least about 60% phenytoin after I hour. The term about herein means ± 5 % of the given value.

The pharmaceutically acceptable hydrophilic polymers used in according with the present invention comprise of carbohydrate gums, cellulose ethers, acrylic acid polymers or mixtures thereof.

Carbohydrate gums may be selected from amongst xanthan gum, tragacanth gum, gum karaya, guar gum, acacia gellan gum, locust bean gum and the like. These gums upon contact with the gastrointestinal fluid form a viscous gel and sustain the release of the drug even when used in very small amounts.

The cellulose ethers used in accordance with the present invention include methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl ethyl cellulose, hydroxypropyl butyl cellulose and the like.

The acrylic acid polymers may be carboxyvinyl polymer such as those available under the brand name Carbopol (B.F. Goodrich, USA).

The hydrophilic polymer(s) may be present in an amount from about 10% to 30% w/w of the composition. The use of small amounts of hydrophilic polymers ensures low total weight of the dosage form and therefore provides the therapeutic dosage of the drug in a single unit as compared to two or three units which need to be administered while using commercially available Dilantin® 100mg capsules. The present invention provides obvious benefits with respect to patient convenience and therefore better patient compliance.

Phenytoin sodium is monosodium salt of 5,5-diphenyl hydantoinate, described on page 1259 of the Twelfth Edition of the Merck Index, which is incorporated herein by reference. It is useful as an anticonvulsant, effective for the treatment of generalized tonic-clonic seizures in adults and children and is also useful in the treatment of simple and complex partial seizures.

Phenytoin sodium used in accordance with the present invention comprises about 40% to about 70% w/w of the total formulation weight.

In addition to the active and hydrophilic polymer(s), the composition of the present invention may contain other excipients, which act in one or more capacities as diluents, lubricants or glidants.

Diluents can be selected from any conventional diluents such as microcrystalline cellulose, powdered cellulose, lactose, starch, mannitol, calcium hydrogen phosphate and dextrose.

Lubricants of the present invention may be selected from talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate and sodium benzoate.

Glidants may be selected from the colloidal silicon dioxide (Aerosil) or talc.

The blend of active, polymer and excipient may be prepared using tumbler mixers, ribbon mixers, twin shell V-blenders, double cone blenders, planetary mixers or fluid bed mixers. This blend is then filled into hard gelatin capsules using either gravity wherein the powder blend is filled into the capsule due to its natural flow; or partial compression, so that weak slugs are formed inside a calibrated punch prior to being deposited into the capsule.

Alternatively, the lubricants and glidants may be added after thorough blending of other components of the formulation. This blend is passed through No. 30 mesh screen and filled into hard gelatin capsules.

The extended release phenytoin capsules of the present invention release the drug both initially and after storage for 3 months at 40 degrees centigrade / 75% relative humidity over a two hour period when measured in vitro by dissolution testing. Dissolution is carried out in 900ml of water using USP Dissolution Apparatus I (basket) at 50 rpm (for 100 mg capsules) and 75 rpm (for 200/300 capsules). 100 mg capsules of present invention show the following in vitro dissolution profile (a) not more than 35 percent drug released in 30 minutes (b) not more than 75 percent drug released in 60 minutes, and (c) not less than 65 percent drug released in 120 minutes whereas 200/300 mg capsules show the following in vitro dissolution profile (a) not more than 40 percent drug released in 30 minutes (b) not more than 65 percent drug released in 60 minutes, and (c) not less than 75 percent drug released in 120 minutes.

The examples given herein further illustrate the invention and are not intended to limit the scope of the invention.

EXAMPLES 1-5

Ingredients	mg/Capsule				
	Ex-1	Ex-2	Ex-3	Ex-4	Ex-5
Phenytoin sodium	300.0	300.0	300.0	300.0	300.0
Xanthan gum	20.0	25.0	20.0	20.0	20.0
Hydroxypropyl cellulose	25.0	35.0	20.0	-	30.0
Hydroxypropyl methylcellulose	75.0	90.0	80.0	100.0	55.0
Microcrystalline cellulose	18.75	18.75	18.75	18.75	18.75
Talc	15.0	15.0	15.0	15.0	15.0
Colloidal silicon dioxide	1.25	1.25	1.25	1.25	1.25
Magnesium stearate	10.0	10.0	10.0	10.0	10.0

Process:

Phenytoin sodium, microcrystalline cellulose, hydroxypropyl cellulose, Xanthan gum and hydroxypropyl methylcellulose are loaded into a twin shell V-blender and blended. Talc, colloidal silicon dioxide and magnesium stearate are added to the blend and mixed. This blend is screened through No. 30 mesh and filled into size "0" hard gelatin capsules on automatic capsule filling machines. These capsules are then packed into high-density polyethylene bottles and stored for 3 months at 40°C / 75% relative humidity and tested for in-vitro dissolution. Table 1 shows the dissolution data of Phenytoin sodium 300mg capsules prepared as per composition of Example 3 initial and after storage for 3 months at 40°C/ 75% relative humidity.

Table 1: In vitro dissolution profile of Phenytoin sodium capsules using USP Apparatus I/900ml water/75 rpm

Time (min)	Percent phenytoin released (%)	
	Initial	After storage for 3 months at 40°C/ 75% RH
30	20.0	22.0
60	42.0	44.0
120	73.0	79.0

EXAMPLE - 6

Ingredients	mg/Capsule
Phenytoin sodium	100.0
Xanthan gum	6.7
Hydroxypropyl cellulose	6.7
Hydroxypropyl methylcellulose	26.7
Microcrystalline cellulose	6.25
Talc	5.0
Colloidal silicon dioxide	0.42
Magnesium stearate	3.33

Process:

Phenytoin sodium, microcrystalline cellulose, hydroxypropyl cellulose, Xanthan gum and hydroxypropyl methylcellulose are loaded into a twin shell V-blender and blended. Talc, colloidal silicon dioxide and magnesium stearate are added to the blend and mixed. This blend is screened through No. 30 mesh and filled into size "0" hard gelatin capsules on automatic capsule filling machines. These capsules are then packed into high-density polyethylene bottles and stored for 3 months at 40°C / 75% relative humidity and tested for in-vitro dissolution.

Table 2 shows the dissolution data of Phenytoin sodium 100mg capsules prepared as per composition of Example 6 using USP Apparatus I, 900ml water at 50 and 75 RPM.

Table 2: In vitro dissolution profile of Phenytoin sodium capsules using USP Apparatus I/900ml water.

Time (min)	Phenytoin released (%)	
	At 50 RPM	At 75 RPM
30	33.0	45.0
60	71.0	79.0
90	91.0	93.0
120	97.0	95.0

WE CLAIM:

1. A process for preparing extended release pharmaceutical composition comprising a blend of phenytoin sodium and hydrophilic polymer(s); wherein the blend forms a matrix on coming in contact with aqueous media, and wherein said matrix retains at least about 20% of phenytoin after 1 hour.

2. The process ~~according~~ to claim 1 wherein the said matrix retains at least 30% of phenytoin after 1 hour.

3. The process according to claim 1 wherein the said matrix retains at least 60% of phenytoin after 1 hour.

4. The process according to ~~claim 1~~ wherein the blend is ~~filled into capsule.~~

5. The process according to claim 4 wherein the blend is filled as powder.

6. The process according to claim 1 wherein the composition comprises from 40 to ~~about~~ 70 percent by weight of phenytoin sodium.

7. The process according to claim 1 wherein the composition comprises from 10 to ~~about~~ 30 percent by weight of hydrophilic polymer(s).

8. The process according to claim 7 wherein the hydrophilic polymer(s) may be selected from carbohydrate gum, cellulose ether, acrylic acid polymer or mixtures thereof.

9. The process according to claim 8 wherein the carbohydrate gum is selected from xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum, locust bean gum or mixtures thereof.

10. The process according to claim 9 wherein the carbohydrate gum is xanthan gum.

11. The process according to claim 8 wherein the cellulose ether is selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl butyl cellulose, carboxymethyl cellulose or combinations thereof.

12. The process according to claim 11 wherein the cellulose ether is hydroxypropyl cellulose.

13. The process according to claim 11 wherein the cellulose ether is hydroxypropyl methylcellulose.

14. The process according to claim 8 wherein the acrylic acid polymer is carboxy vinyl polymer.

15. The process according to claim 8 wherein the hydrophilic polymer(s) is a combination of a cellulose ether and carbohydrate gum.

16. The process according to claim 15 wherein the cellulose ether is a combination of hydroxypropyl cellulose and hydroxypropyl methylcellulose and carbohydrate gum is xanthan gum.

17. The process according to claim 1 wherein the composition may contain other pharmaceutically acceptable excipients in addition to phenytoin sodium and hydrophilic polymer(s).

18. The process according to claim 17 wherein the pharmaceutically acceptable excipients are selected from diluents, lubricants and glidants.

19. The process according to claim 18 wherein the diluents may be selected from microcrystalline cellulose, powdered cellulose, lactose, starch, mannitol, calcium hydrogen phosphate and dextrose.

20. The process according to claim 19 wherein the diluent is microcrystalline cellulose.

21. The process according to claim 18 wherein the lubricant may be selected from talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium stearyl fumarate and sodium benzoate.

22. The process according to claim 21 wherein the lubricant is magnesium stearate.

23. The process according to claim 21 wherein the lubricant is talc.

24. The process according to claim 18, wherein the glidant may be selected from colloidal silicon dioxide and talc.

25. The process according to claim 24 wherein the glidant is colloidal silicon dioxide.

26. The process according to claim 1 wherein phenytoin sodium, hydrophilic polymer(s) and the diluent are blended; lubricants and glidant are added to the blend and mixed; the blend is screened, and filled into hard gelatin capsules on automatic capsule machine.

27. The process according to claim 1 wherein said composition has the following in vitro dissolution profile when tested using USP Apparatus I in water at 75 rpm:

a. not more than 35 percent released in 30 minutes,

b. between 30 and 75 percent released in 60 minutes

c. not less than 65 percent released in 120 minutes.

28. A process for preparing extended release phenytoin sodium capsule comprising a blend of the phenytoin sodium, xanthan gum, hydroxypropyl cellulose, hydroxypropyl methylcellulose, wherein the blend forms a matrix on coming in contact with aqueous media, and wherein said matrix retains at least about 20% of phenytoin after 1 hour.

Dated this **16TH** day of **December, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to an extended release pharmaceutical composition and a process of making it. The extended release pharmaceutical composition comprises a blend of phenytoin sodium and hydrophilic polymer(s), wherein the blend forms a matrix on coming in contact with aqueous media, and wherein said matrix retains at least about 20% phenytoin after 1 hour.